REMARKS

The Office Action rejected Claims 35-39 under 35 USC § 102 (e) as defining subject matter which is allegedly anticipated by the teaching in U.S. Patent No. 6,028,102 to Bialer et al ("Bialer et al."). Furthermore, Claims 35-43, 47-49, 54, 57, and 68-72 are rejected under 35 USC § 103 as defining subject matter which is allegedly rendered obvious by the teachings in U.S. Patent No. 5,378,729 to Kohn et al in view of an article by Post, et al., in Psychopharmacology 1996, 128, 115-129 ("Post et al.") or an article by Yang et al. in Psychiatry and Clinical Neurosciences, 1998, 52 (4), 429-431 ("Yang et al.") or an article by Keck, et al in J. Neuropsychol and Clinical Neurosciences, 1992, 4, 395-405 ("Keck et al."). Claim 35 is further rejected under 35 USC § 103 as defining subject matter, which is allegedly rendered obvious by the teachings in U.S. Patent No. 6,716,810 to Brennan, et al (Brennan, et al."). In addition, Claim 35 is rejected under 35 USC § 103 as defining subject matter which is allegedly rendered obvious by the teachings in U.S. Patent No. 6,511,963 to Maccecchini ("Maccecchini") Claim 35 is rejected under 35 USC § 103 as defining subject matter which is allegedly rendered obvious by the teachings in U.S. Patent No. 6,034,216 to Somers et al ("Somers et al.")

Applicant has amended the claims, cancelled others and added claims, which when considered with the comments hereinbelow are deemed to place the present case in condition for allowance. Favorable action is respectfully requested.

At the onset, before addressing the merits, it is to be noted that the applicant has amended the claims. The amendment to the claims is supported by the underlying disclosure. For example, Claim 35 has been amended to restrict the variable "n" to 1. Support for n being 1 is found on Page 25, Line 20 of the instant specification. Moreover it should be noted that applicant has amended Claim 35 by specifically reciting the electron withdrawing groups and

electron donating groups therein for R and R_1. Support for this aspect of the amendment to Claim 35 is found on Page 20, lines 7-31 of the instant specification. In view of this amendment, R and R_1 cannot include peptides or other amino acids. Further Claim 35 has been amended to restrict the scope thereof to R being aryl lower alkyl, which may be unsubstituted or substituted on the aryl moiety with the described electron withdrawing group or electron donating group and R_1 being lower alkyl which may be unsubstituted or substituted with the described electron withdrawing group or electron donating group. Support is found on page 25, line 31 to page 26, line 12 of the instant specification. The definitions of R_2 and R_3 have also been narrowed. Support is found on page 15, line 26 to page 17, line 29, page 23, line 1 to page 25, line 30 of the instant specification.

In addition, R_3 has been amended to recite that only R_2 includes hydrogen in its definition. Support is found in the instant specification for such an amendment. Attention is directed to Claim 36 as originally filed, which states that one of the R_2 and R_3 is hydrogen; this means that the other is not hydrogen. Thus, there is support in the application for one of R_2 and R_3 to be defined as other than hydrogen. Thus, applicant has amended the claims so that R_3 excludes hydrogen from its definition. Claims 36 and 40-43 have been amended to be consistent with the claimed subject matter.

Applicant has also added Claims 73-106 to the application. Support for Claim 73 is found in the original Claim 63. Support for Claim 74 is found on Page 25, lines 31-32 of the present specification. Further, support for Claims 75-88 is found on Page 26, line 24 to Page 29 line 16 of the instant application.

Applicant has also added claims 85-102 to the instant application. Support for Claims 85-102 is found on page 20, line 1 to page 23, line 23 and page 24, line 3 to page 27, line 10 of the instant application.

These amendments also deleted subject matter. Applicant has not abandoned this subject matter and reserve the right to file a continuation application directed thereto.

No new matter is added to the application. Moreover, these amendments were effected to make the claimed subject matter to be directed to preferred embodiments.

In support of the rejection of Claims 35-39 under 35 USC § 102 (e), the Office Action cites Bialer et al.

Bialer allegedly discloses that the following glycine derivative can be used to treat bipolar disorders:

$$Ac\text{-}NH\text{-}{*}CH_2\text{-}CONH\text{-}CH_2\text{-}C_6H_5$$

It is to be noted that the carbon atom which is marked with an asterisk contains two hydrogen atoms. On the other hand, the corresponding carbon atom in the formula in the instant claims cannot be substituted by two hydrogen atoms. More specifically, the corresponding carbon atoms in the formula recited in Claims 35 and 86 is substituted by the groups R_2 and R_3. As defined, both R_2 and R_3 cannot be hydrogen. Although R_2 can be hydrogen, the definition of R_3 excludes hydrogen. Thus, the claimed subject matter of the present invention does not encompass the use of $Ac\text{-}NH\text{-}CH_2\text{-}CONH\text{-}CH_2\text{-}C_6H_5$ for treating bipolar disease. Therefore the rejection of Claims 35-39 under 35 USC § 102 (e) is obviated; withdrawal thereof is respectfully requested.

In support of the rejection of claims 35-43, 47-49, 54, 57 and 68-72 under 35 USC §103, the Office Action cites Kohn et al. in view of Post et al., Yang, et al. or Keck, et al.

Applicant agrees with the Office Action that Kohn et al disclose the compounds to which the claims are directed. Moreover, as indicated in the Office Action, Kohn et al disclose that these compounds are anticonvulsants. There is no teaching or suggestion that therein that these compounds can be used to treat bipolar disorders. The Office Action concurs.

The Office Action, however, alleges that the secondary references disclose that anti-convulsants can be used to treat bipolar disorders. In other words, the Office Action is assuming that all anticonvulsants can also be used to treat bipolar disorders. Based on this assumption, the Office Action concludes that it would have been obvious for the compounds disclosed in the aforementioned claims to be useful for treating bipolar disorders.

However, the assumption by the United States Patent and Trademark Office is not correct. Merely because a compound possesses anti-convulsant activity does not signify that it is useful in treating bipolar diseases. Attention in this vein is directed to an article entitled, "Anticonvulsants in Bipolar Disorders", by Singh et al, in Psychiatr Clin N. Am. 2005, 28, 301-323 ("Singh et al"). Gabapentin is a known anti-convulsant. However, as described therein on page 315, and concluded on page 320 thereof, gabapentin ("GBP") has little or no specific effect in bipolar disorder. Thus, they do not recommend the use of GBP as monotherapy in the long term treatment of bipolar disorder. In fact, as concluded on Page 320, "there is consensus" [among scientists] that some anti-convulsants "have little or no specific effect in bipolar disorder". Thus, one can not conclude that a compound which is characterized as an anti-convulsant can also be used to treat bipolar disorder. At best, it could be said that it would be obvious to try to use an anti-convulsant treating bipolar disease, but as the courts have held, obvious to try is not the proper standard under § 103. In re Geiger, 815 F2d 686, 688, 2 USPQ 2d 1276, 1278 (Fed. Cir 1987). Thus, for the reasons given, the rejection of Claims 35-43, 47-

49, 54, 57, and 68-72 under 35 USC § 103 is obviated, withdrawal thereof is respectfully requested.

In support of the rejection of Claim 35 under 35 USC § 103, the Office Action cites Brennan et al.

Brennan et al disclose both cyclic and non-cyclic N-acetylated peptides for regulating body weight and/or regulating the rate of weight gain or loss and particularly for preventing obesity. The peptides disclosed therein contain several linear amino acids. The Office Action refers to the examples in Column 10, line 20, Column 24, line 39 and Column 27, line 35 in its support of the rejection. However, each of these examples have several linear peptide bonds. On the other hand, the compounds used in the present invention do not have any linear peptide bonds between R and the NH groups and between R_1 and the acyl group. More specifically, in the compounds utilized in the present invention, there is no amide linkage between R and the NH group or between R_1 and the acyl group. As defined, R is unsubstituted or substituted aryl lower alkyl and R_1 is defined as unsubstituted or substituted lower alkyl. Thus, there is no peptide linkage between the acyl group and R_1 or between R and the NH group. Therefore, the compounds used in Brennan et al. are not similar to the compounds used in the present invention. Consequently, the teachings of Brennan et al do not suggest the compounds used in the present invention.

Moreover, contrary to the allegations of the Office Action, Brennan et al do no teach or disclose that the compounds therein can be used to treat bipolar diseases. The Office Action refers to the disclosure on Column 55, Line 25 of Brennan et al, but the passage does not indicate that the compounds therein are useful for treating bipolar disorders. On the contrary, it discloses that the compounds therein are useful in ameliorating the weight gain side effect which can result

from the administration of pharmaceuticals for treating, inter alia, bipolar disorders. Thus, Brennan et al do not teach, disclose or suggest compounds for treating bipolar disorders. Consequently, it fails to teach or suggest that compounds of the present invention can be used to treat bipolar disorders. Thus, inasmuch as Brennan et al do not teach or suggest the compounds used in the present invention and fail to suggest the utility of bipolar disorders, the present invention is patentable thereover. Thus, the rejection of Claim 35 under USC § 103 is obviated, withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claim 35 under 35 USC § 103, the Office Action cites Maccecchini. It discloses various peptides in Tables I and II containing several amino acids and several linear peptide bonds. However, as indicated hereinabove, the compounds used in the present invention do no have any peptide linkage between the acyl group and R_1 or between R and the NH group. As defined, R and R_1 cannot be amino acids or contain amino acids. More specifically as defined R is unsubstituted or substituted lower arylalkyl and R_1 is unsubstituted or substituted lower alkyl, neither of which are amino acids as defined. Further neither R nor R_1 contain an amino acid substituent. Therefore, as defined the compounds used in the present invention do not contain a peptide bond between the R group and the amino group or between the R_1 group and the acyl group. Thus, the compounds in this reference are structurally quite different from the compounds utilized in the present invention. Thus, Maccecchini do not teach, disclose or suggest the use of the compounds utilized in the present invention for treating bipolar disorders. Therefore, the rejection of Claim 35 under USC § 103 is obviated, withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claim 35 USC § 103, the Office Action cites Somers et al. The Office Action refers to the compound Acetyl-D-ß-Nal- ß -Nal- ß -Nal-[N-3-amino propyl]

amide, and alleges that this compound falls within the scope of the claims. However, the compound contains several linear peptide bonds. As indicated hereinabove, the compounds in the present invention do not have any peptide linkages between the acyl group and R_1 or between R and NH. Thus, Somers et al do not teach, disclose or suggest the use of the compounds used in the present invention.

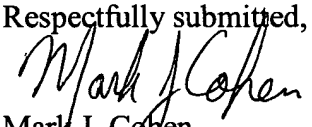
The Office Action admits that Somers, et al do not teach or suggest that the compound therein are useful for treating bipolar disorders. Bipolar diseases is not listed in Somers et al as one of the diseases for which the compounds therein as useful. See Column 29 thereof. However, the Office Action alleges that a patient suffering from bipolar disorder experiences episodes of depression, and it concludes that a teaching that a drug useful for the treatment of depression would suggest to one of ordinary skill in the art that it would be useful for the treatment of bipolar disorder. Applicant disagrees; depression is not the same as bipolar disorder. Bipolar disorder is defined as a form of mood disorder characterized by a variation of mood between a phase of manic or hypomanic elation, hyperactivity, and hyer imagination, and a depressive phase of inhibition, slowness to conceive ideas and move, and anxiety or sadness.

Bipolar disorder is broadly treated by the class of drugs known as mood stabilizers, which are used to prevent or mitigate all disease symptoms. On the other hand, antidepressant drugs only have a potential benefit, at best, for treating the depressive symptoms that occur to varying degrees in bipolar patients. They do not treat nor are they intended to treat the change in the mood disorders characteristic of bipolar disorder. Consequently, although a drug claiming to treat depression may potentially alleviate some of the manifestations of bipolar disorder, it does not provide an effective treatment for the disease itself. Such treatment, however, is one of the utilities for the compounds claimed in this application.

The fact that the compounds in Somers et al. are useful for treating depression thus does not, in any way, give any suggestion that the same compounds would be useful for treating bipolar disorder. There is no teaching or suggestion in Somers et al that correlates treatment of depression with treatment of bipolar disorder. Inasmuch as, Somers et al do not teach, disclose or suggest the use of the compounds described in the present invention, and do not disclose or suggest that the compounds therein are useful for treating bipolar disorder, Somers et al do not disclose or suggest the present invention recited in Claim 35. Consequently, for the reasons given here, the rejection of Claim 35 under 35 USC § 103 is obviated, withdrawal thereof is respectfully requested.

Therefore, in view of the amendments to the claims and the remarks herein, it is respectfully submitted that the present case is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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Anticonvulsants in Bipolar Disorder

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Bipolar disorder is a life-threatening illness that is complex and challenging to treat acutely and to manage long-term. The past decade has seen the emergence of anticonvulsants or antiepileptic drugs (AEDs) as viable and safe pharmacologic options in acute and long-term management of bipolar disorder. In addition, there has been a shift in focus from acute or episodic control of symptoms to the long-term management and prevention of further mood episodes that could worsen the course of illness.

The underlying pathophysiologic mechanisms in bipolar disorder are poorly understood. Evidence from preclinical studies suggests that bipolar disorder may share some biologic mechanisms with epilepsy. It has been hypothesized that an imbalance between the excitatory (primarily glutamate) and inhibitory (mainly γ-aminobutyric acid [GABA]) amino acids and dysfunctional cation pumps (sodium and calcium channels) may be involved in the pathogenesis of both epilepsy and bipolar disorder [1]. Bipolar disorder is characterized by recurrent episodes of mania or hypomania, either concomitantly or in alteration with a depressive episode. The characteristic episodic pattern of epileptic supports the hypothesis that bipolar disorder and epilepsy share a common pathophysiologic process. Earlier observations of the antimanic property of carbamazepine, an anticonvulsant, led to the proposal by Post and colleagues [2] that epilepsy and bipolar disorder could be conceptualized as sharing a common underlying biologic mechanism

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called kindling. In kindling, repeated subthreshold neuronal stimulation generates an action potential sufficient to induce a seizure in epileptic patients and different mood states—mania, depression, or mixed states—in patients with bipolar disorder. It was then proposed that the progression of bipolar illness could be conceptualized by an animal model of kindled seizures and that this model could be used to screen antiepileptic drugs as candidate therapeutic agents for the treatment of bipolar illness [1]. Although this hypothesis was viewed at the time as scientifically appealing, it has never been confirmed or supported by empiric human clinical data.

This article reviews the role of the AEDs in the treatment of bipolar disorder with a special focus on data from randomized, placebo-controlled studies. It focuses on the role of valproate or divalproex sodium (DIV), carbamazepine (CBZ), oxcarbazepine (OXC), and lamotrigine (LAM) in the acute and long-term treatment of bipolar disorder and summarizes acute and longitudinal data on the newer anticonvulsants, gabapentin (GBP), topiramate (TMP), zonisamide (ZON), levetiracetam (LEV), and phenytoin (PHT), in bipolar disorder. It reviews the literature about the pharmacologic profiles (Table 1), safety, and tolerability of each of the AED.

Valproate or divalproex sodium

DIV has a potent action on the GABA system and, to a lesser extent, possesses antiglutamatergic properties [3]. Serendipitously, DIV was noted to possess behavioral effects in patients with bipolar disorder [4]. Following a large, confirmatory, randomized, double-blind, placebo parallel-group clinical trial of DIV versus lithium versus placebo in 1994, DIV was approved by the United States Food and Drug Administration (FDA) for the treatment of acute mania in 1995.

Acute efficacy

Acute mania

The antimanic efficacy of DIV has been compared in different studies to placebo, lithium, and haloperidol [5–8]. DIV demonstrated significant superiority to placebo (53% versus 10% response rates) in the first preliminary parallel-design, placebo-controlled study conducted by Pope et al [6]. Subsequently, Bowden and colleagues [7] conducted a large, three-arm study, comparing DIV to placebo, with lithium as the active comparator. The response rates in the DIV, lithium, and the placebo groups were 48%, 49%, and 25%, respectively. DIV demonstrated superior efficacy, compared with lithium, in a subset of patients with mixed mania [9] and in patients whose mania was associated with depressive symptoms [10]. This finding was also noted in another parallel-group study conducted by Freeman et al [11]. In the study by Bowden et al [7], which used an unbalanced study design, DIV also demonstrated better tolerability than lithium, and there

Table 1
Comparative pharmacologic profiles of anticonvulsants used in bipolar disorder

	DIV	CBZ	OXC	LAM	GBP	TMP	ZON	LEV	PHT
Time to steady state (d)	1–3	21–28[a]	2	3–15	1–2	4–5	5–15	2	7–28
Half-life (h)	9–16	12–17[b]	2–9[c]	25–30	5–7	19–23	63	6–8	7–22
Bioavailability (%)	>95	85	100	98	60–27[d]	80	100	100	100
Protein binding (%)	90–95	40–90	40	40–50	0–3	13–17	40	<10	93–98
Metabolism	Liver	Liver	Liver/biliary	Liver	None	Minimal	Liver	Liver	Liver
Clinically relevant metabolite	2-propyl-4-pentenoic acid (may cause toxicity)	10,11-epoxide (clinically active and may cause toxicity)	10-hydroxy carbazepine (clinically active)	None	None	None	None	None	None
Excretion	Renal	Renal	Renal	Renal	Renal	Renal	Renal	Renal	Renal
Dosage range (mg/d)	200–2500	200–1200	300–2400	50–400	600–3600	100–600	100–600	1000–3000	100–400
Target blood levels (μg/mL)	50–125	6–12	10–35	N	N	N	10–40	N	10–20
Monitoring of drug levels	R	R	NR	NR	NR	NR	NR	NR	NR
Monitoring of liver functions	R	R	NR	NR	NR	NR	NR	NR	NR
Monitoring of renal functions	NR	NR	NR	NR	NR	R	NR	NR	NR
Monitoring of blood counts	R	R	NR	NR	NR	NR	NR	NR	NR
Monitoring of lipids	NR	NR	NR	NR	NR	NR	NR	NR	NR
Monitoring of blood sugar	NR	NR	NR	NR	NR	NR	NR	NR	NR
US-FDA pregnancy category	D	D	C	C	C	C	C	C	D

Abbreviations: CBZ, carbamazepine; C_{max}, time to peak plasma concentration; DIV, valproate or divalproex; GBP, gabapentin; LAM, lamotrigine; LEV, levetiracetam; N, not defined; NR, not required; OXC, oxcarbazepine; PHE, phenytoin or fosphenytoin; R, required; TMP, topiramate; ZON, zonisamide.

From Refs. [1,43,55,66].

[a] For completion of autoinduction.

[b] Because of autoinduction.

[c] 2 hours for parent compound, 9 hours for active metabolite.

[d] 60% at 900 mg/d in divided doses and progressively decreases to 27% at 4800 mg/d in divided doses.

were fewer dropouts in the DIV group than in the placebo group. DIV was similarly more efficacious than haloperidol in patients with psychotic mania [8] and to olanzapine in two studies [12,13].

DIV is effective when used in combination with other medications used in the treatment of mania, as demonstrated by several randomized, double-blind, placebo-controlled studies. Three of these studies, involving the addition of an antipsychotic drug to either DIV or lithium, demonstrated that the combination groups required lower doses of the antipsychotic drug in comparison to monotherapy with an antipsychotic [13–15]. The addition of DIV to haloperidol led to greater improvement in symptoms of mania than did haloperidol alone [16]. The response rate was similarly greater when either risperidone [14,15] or olanzapine [13] was added to DIV or lithium than when the mood stabilizers were continued as monotherapy. In the study by Sachs et al [14], patients enrolled had been either nonresponsive after receiving monotherapy with lithium or DIV at an adequate dose for 2 weeks or longer (add-on therapy group) or had been in a manic state without any treatment. In the latter group, treatment with risperidone and either lithium or valproate was initiated concomitantly (cotherapy group). Analysis of the data did not show any advantage for the combination treatment in the cotherapy group, but add-on therapy was advantageous in the group of patients who did not respond to DIV or lithium monotherapy. Each of the other studies required some degree of failure with monotherapy before addition of the second medication. Hence, these studies suggest that combination therapy is indicated in patients who have had no response or partial response to a short period of adequate treatment with a first antimanic drug.

Bipolar depression

A small, blinded, randomized study demonstrated equivalent efficacy when DIV, paroxetine, or lithium was added to lithium (n = 19) or DIV (n = 8) in patients with bipolar depression. DIV was added to the regimen of patients taking lithium, lithium was added for patients taking DIV, and paroxetine was added to either lithium or DIV. The rate of discontinuation was lower in the group receiving paroxetine plus mood stabilizer than in the group taking DIV plus lithium [17,18]. A double-blind, parallel-group, placebo-controlled study (n = 45) to assess the efficacy of DIV in acute bipolar depression included subjects meeting *Diagnostic and Statistical Manual IV* criteria for bipolar disorder types I or II and criteria for a current major depressive episode [19]. This study included a 14-day, single-blind, placebo lead-in phase followed by an 8-week, double-blind, treatment phase and then an open-treatment phase of up to 8 weeks. Patients were considered recovered if there was absence of hypomania (Young Mania Rating Scale [YMRS] < 10) and an improvement of 50% or more on the 26-item Hamilton Depression Rating Scale (HDRS). Forty-three percent of the patients treated with DIV (9/21) met criteria for recovery compared

with 27% of the patients treated with placebo (6/21). At every follow-up assessment, the patients treated with DIV demonstrated more improvement on the HAM-D depressed mood item than patients taking placebo, and this difference reached statistical significance at weeks 2, 4, and 5. Results from two other preliminary studies suggest that DIV is efficacious in the acute management of recurrent major depression and combat-related posttraumatic stress disorder [20,21].

DIV may have better efficacy in preventing depressive episodes or depressive symptoms during long-term treatment than in treating acute bipolar depression [18]. In a randomized, double-blind, parallel-group study over a 52-week maintenance period, bipolar type I patients were assigned to DIV, lithium, or placebo. The use of adjunctive sertraline or paroxetine was allowed for breakthrough depression. In the subgroup of patients taking the antidepressants, significantly more patients taking placebo than DIV discontinued treatment early because of depression. Patients taking DIV had less worsening of depressive symptoms than the subgroup of patients taking lithium, and they had a lower probability of relapse into depression, particularly if they had demonstrated a response to DIV when manic [22].

Maintenance efficacy

In a large, double-blind, placebo-controlled study [23], patients with bipolar disorder type I (n = 372) were randomly assigned to 1 year of maintenance treatment with DIV, lithium, or placebo after meeting recovery criteria within 3 months of an index manic episode. The time to develop any new full mood episode, the primary measure of efficacy, did not differ significantly among the treatment groups, although there was a trend of superiority for the DIV group. Secondary measures included time to a manic episode, time to a depressive episode, and Global Assessment of Function scores. The DIV group, when compared with placebo, had lower rates of early discontinuation for onset of any mood episode, onset of a depressive episode, and dropout for any reason [22,18]. DIV was superior to lithium in prolonging the duration of successful prophylaxis in the study, with less worsening of depressive symptomatology and Global Assessment of Function scores.

A separate 47-week maintenance study in bipolar patients with an index episode of acute mania found no significant differences between DIV and olanzapine in the rates of manic relapse or in the median time to a manic relapse [13].

Dosage and serum-level monitoring

Patients with serum levels greater than 45 μg/mL were significantly more likely to have at least 20% improvement in manic symptomatology than

patients whose serum level was lower than 45 μg/mL [18,24]. During maintenance treatment, valproate levels between 75 and 100 μg/mL were more likely to maintain prophylaxis than serum levels higher or lower than this range. Another study showed that adjustments of DIV dosing based on serum valproate levels were associated with a reduction in length of hospital stay [25].

Tolerability

DIV is well tolerated, as evidenced in the largest maintenance trial with DIV, in which reported weight gain and tremors were the only symptoms seen more commonly with DIV than with placebo [23]. Common dose- or serum level–related side effects seen with DIV include tremors (9% to 22%) [26], sedation (24%) [26], reduction in platelets (1%–32%) [27] and white blood cell count (0.4%) [27], nausea (22%), vomiting (14%), and alopecia (2%–22%). Extremely low rates of hepatotoxicity (1/49,000) and pancreatitis (<1%), which are idiosyncratic in nature and more commonly seen in younger patients, do not justify the routine monitoring of hepatic function and amylase levels. DIV is FDA pregnancy category D and has been associated with neural tube defects (1%–4%) [18].

Carbamazepine

CBZ has been hypothesized to reduce kindling, enhances GABAergic transmission, and has antiglutamatergic properties in addition to its cellular and intracellular actions [3]. It was the first AED widely used in the treatment of bipolar disorder.

Acute efficacy

Acute mania

Sixteen controlled trials have been conducted to assess the efficacy of CBZ in acute mania, but the interpretation of the results of many of these studies is difficult. Early trials were limited by the absence of a parallel placebo group, small sample sizes, and the use of other antimanic drugs during the study [28–30]. Recently, in the first large, randomized, double-blind, placebo-controlled trial using extended-release CBZ capsules (ERC-CBZ) in acute mania, ERC-CBZ demonstrated superior efficacy to placebo (response rate 41.5% versus 22.4%) with significant improvement in mixed manic patients. In addition to demonstrating ERC-CBZ's efficacy, the study showed that it is well tolerated. Pooled data from five randomized, double-blind, controlled trials of CBZ in acute mania have demonstrated equivalent responses with CBZ, lithium, and chlorpromazine (50%, 56%, and 68% respectively) [29].

Bipolar depression

Although a moderate antidepressant effect was seen in a placebo-controlled trial of CBZ monotherapy, this study was limited by its small sample size (n = 13) and the inclusion of patients with diagnosis of schizoaffective disorder, bipolar type and unipolar depression in addition to patients with bipolar disorder [31,32]. In a study of 35 patients with bipolar depression, Post and colleagues [33] reported that 57% experienced mild improvement, and 34% marked improvement (average dose, 971 mg/day). These preliminary data suggest that CBZ may possess some acute antidepressant efficacy, but more rigorously controlled investigation of its antidepressant efficacy is needed.

Maintenance efficacy

There is a paucity of data on the efficacy of CBZ in long-term management of bipolar illness [34]. In the only placebo-controlled study to assess the maintenance effectiveness of CBZ in bipolar disorder, CBZ demonstrated significant superiority to placebo [35]. An open-label, 2.5-year, randomized maintenance study found lithium to be superior to CBZ using broader efficacy measures that included time to relapse, time to receiving additional medications, or intolerance. There was no difference between the two groups on the primary efficacy measure, time to rehospitalization for a new mood episode. CBZ demonstrated superior efficacy in patients with atypical forms of mania [36,37]. When functional improvement is used as a measure, a combination of lithium and CBZ is more effective than either agent used as monotherapy [38].

Dosage and serum-level monitoring

Because of CBZ's induction of its metabolism and the associated adverse events relating to the central nervous system, particularly in the early course of treatment, CBZ should be started at low doses (100–400 mg/day) and increased gradually until response or adverse events ensue or serum levels exceed 12 μg/mL [3]. Correlation between serum level and response to CBZ has not been established in bipolar disorder.

Tolerability

The acute and long-term utility of CBZ is limited significantly by its side-effect profile. The discontinuation rate because of adverse events in a randomized, double-blind, crossover maintenance study was higher in the CBZ group (22%) than in the lithium group (4%) [38]. Dose-related adverse effects with CBZ include dizziness, sedation, ataxia, diplopia, and nystagmus, all of which are reversible [28]. CBZ is associated with a mild rash in 10% of the patients, which may be the harbinger of a life-threatening Stevens-Johnson syndrome. Agranulocytosis and aplastic anemia, idiosyncratic

in nature, occur in 1/10,000 to 1/100,000 patients; benign leukopenia (transient in 10% of patients and persistent in 2%) is more common. Thrombocytopenia occurs in 2% of patients treated with CBZ. CBZ may also cause mild hyponatremia, which may manifest more seriously in geriatric or medically ill patients. The side effects associated with CBZ are attributed to its major metabolite, CBZ-(10;11)-epoxide.

CBZ, by its induction of the cytochrome P450 enzymes, particularly P450-3A4, causes lowering of plasma levels of other drugs such as anticonvulsants (DIV, LAM, ZON, TMP, CBZ, PHT, OXC, and others) antipsychotics (aripiprazole, clozapine, haloperidol, olanzapine, risperidone, ziprasidone, and others), antidepressants (bupropion, citalopram, tricyclic antidepressants), anxiolytics/sedatives (buspirone, clonazepam, alprazolam, and others), stimulants (methylphenidate, modafinil) and oral contraceptives [28,39]. To maintain their continual efficacy, higher doses of medications such as oral contraceptives must be used when they are taken concomitantly with CBZ.

CBZ's limited clinical utility and its role as an alternative rather than a first-line treatment option in bipolar illness can be attributed to its propensity to cause drug–drug interactions, its FDA pregnancy category D drug classification, and lack of an FDA indication in bipolar disorder [28].

Oxcarbazepine

OXC is a 10-keto derivative of CBZ, and it is hypothesized that its structural similarity to CBZ bestows on it similar mechanistic actions [28] and similar effects in bipolar disorder. It is free of some of the side-effect and drug–drug limitations associated with CBZ. It is postulated that OXC's efficacy in bipolar illness results from its ability to block voltage-sensitive Na^+ and to modulate voltage-activated Ca^{++} currents [39].

Acute efficacy

Acute mania

Two blinded studies, each lasting 15 days, comparing OXC with active comparators lithium and haloperidol, demonstrated equivalent efficacy in the treatment of acute mania [39,40]. In the first study comparing OXC ($n = 17$) with haloperidol ($n = 20$), 16 of 17 patients receiving OXC showed improvement, whereas improvement was seen in 15 of 20 patients taking haloperidol. OXC was superior to haloperidol in tolerability (rate of adverse events, 10% versus 35%). In a comparison with lithium, 27 of 29 patients taking OXC showed improvement, whereas 22 of 24 patients taking lithium improved. Small sample sizes and the absence of a placebo group limit conclusions from these studies.

Bipolar depression

No studies have been conducted to date to asses the efficacy of OXC in bipolar depression, although OXC's efficacy in two animal models of depression, learned helplessness and forced swimming [39], suggest efficacy in depression.

Maintenance efficacy

There is a lack of direct evidence for OXC in the long-term management of bipolar disorder, with only 12 patients enrolled in long-term studies using OXC [28]. Given the similarities in mechanism of action between CBZ and OXC, it may be hypothesized that CBZ and OXC have similar spectra of activity in bipolar disorder.

Dosage and serum-level monitoring

The doses for OXC are about 50% higher than doses for CBZ, and it is usually dosed between 900 to 2400 mg/day. The serum concentration for OXC recommended for treatment in epilepsy is usually between 10 and 35 μg/mL. As with CBZ, the dose of OXC should be titrated until response is attained or adverse events ensue, with the serum-concentration range used as guide, particularly in regards to pharmacologic safety.

Tolerability

OXC has therapeutic and adverse effects similar to CBZ [28] but is better tolerated than CBZ, perhaps because of its minimal protein-binding property and the absence of the active epoxide metabolite [41]. OXC has a lower propensity to cause leukopenia, agranulocytosis, rash, induction of its own metabolism, and drug–drug interaction [2,39,42]. Averse events commonly seen with OXC include somnolence, dizziness, diplopia, nausea, and ataxia [43]. Because OXC does not cause aplastic anemia and agranulocytosis, hematologic monitoring is not warranted. OXC has a higher incidence of hyponatremia (2.5%) than CBZ, and about 25% to 30% of patients with a hypersensitivity to CBZ experience a reaction to OXC [39,44]. OXC, like CBZ, lowers plasma levels of oral contraceptives, necessitating higher doses of contraceptives or use of alternative contraception for continued protection from pregnancy. OXC is a FDA pregnancy category C drug.

Lamotrigine

LAM inhibits the flux of sodium at use-dependent and voltage-sensitive N^+ channels and has antiglutamatergic action, which may explain its efficacy in the treatment of bipolar disorder. Anecdotal reports of its

beneficial effects on mood during its development as an anticonvulsant led to investigation of its usefulness in the treatment of bipolar disorder.

Acute efficacy

Acute mania

LAM has been shown not to possess efficacy in the treatment of acute mania [45,46] and is not recommended as either monotherapy or as an adjunct to another antimanic agent in this mood state.

Bipolar depression

One large-scale, placebo-controlled trial has demonstrated LAM's efficacy in the acute treatment of bipolar depression. One hundred ninety-five bipolar I patients meeting criteria for a major depressive episode were randomly assigned to treatment with LAM (50 mg/day), LAM (200 mg/day), or placebo in a 7-week, multicenter, double-blinded, placebo-controlled study conducted by Calabrese et al [47]. Patients in the LAM, 200 mg/day, group had a significant improvement in depressive symptomatology as measured by the Montgomery-Asberg Depression Rating Scale, HAM-D 17, CGI-Severity scale, and CG I-Improvement scale as compared with placebo. Improvement was seen as early as week 3 in both the active treatment groups compared with placebo. On several measures, the efficacy of LAM, 50 mg, was similar to placebo. No significant differences in the rates of switch into mania, hypomania, or a mixed state were observed between the LAM and placebo groups (4.6%–5.4% versus 5%) without concomitant medications. In a second randomized, 6-week, placebo-controlled trial [48] using a crossover design in treatment-refractory bipolar ($n = 25$) and unipolar ($n = 6$) patients, a significantly greater number of patients had substantial reduction in depressive symptomatology with LAM than with placebo (45% versus 19%). Secondary analysis of these data with an expanded cohort ($n = 45$) revealed that response to LAM was associated a diagnosis of bipolar disorder, fewer prior hospitalizations, fewer previous medication trials, and male gender.

The studies discussed here demonstrate acute efficacy of LAM in the treatment of bipolar depression, the most common mood state in this illness. In addition, LAM may be a safer alternative to antidepressants, as long as patients do not develop serious rashes, because it does not cause cycle acceleration, mixed states, or switching to mania or hypomania, which worsen long-term prognosis.

Maintenance efficacy

LAM was the second agent approved by the FDA for maintenance treatment in bipolar disorder. This approval followed two paired, randomized, parallel-group, placebo-controlled, multicenter studies that

demonstrated its efficacy in maintenance treatment in patients with bipolar I disorder [49,50]. The two studies were designed to assess the efficacy and tolerability of LAM and lithium compared with placebo for preventing relapse or recurrence of any mood episode in bipolar I patients. Both studies consisted of a screening phase of up to 2 weeks; an open-label phase of to 8 to 16 weeks during which treatment with LAM (100–200 mg/day) was started as monotherapy or adjunctive treatment and other psychotropic agents were gradually tapered off; and an 18-month double-blind phase during which patients were randomly assigned to LAM (100–400 mg/day), lithium (flexibly dosed to achieve blood levels of 0.8–1.1 mEq/L), or placebo. The first study included patients with a recent episode of mania or hypomania (n = 175) [49]. The second study included patients with a recent major depressive episode (n = 463) [50]. The primary efficacy measure in both the studies was time to intervention for any mood episode. In both studies, both LAM and lithium were superior to placebo. In addition, in both studies, LAM, but not lithium, was superior to placebo in delaying relapse in depression; the opposite was true for delaying time to relapse in mania. In a planned, pooled combined analysis of the two studies, both LAM and lithium were significantly more efficacious than placebo on the primary efficacy measure, time to intervention for any mood episode. Whereas LAM, but not lithium, demonstrated superiority to placebo in prolonging time to a depressive episode, both LAM and lithium were more efficacious than placebo in prolonging time to a manic, hypomanic, or a mixed episode. Patients taking LAM had a higher risk of a recurrence or relapse to an episode of the same polarity than of an opposite one [51]. There was no difference between LAM and placebo in the rate of switching to mania, hypomania, or mixed states (5% versus 7%).

In a large, 26-week, placebo-controlled trial in patients with rapid cycling subtype of bipolar disorder (n = 182), LAM (100–500 mg/day) did not separate from placebo in the primary outcome measure, time to intervention with additional pharmacotherapy for an emerging mood episode, in the general cohort of patients and in those with bipolar I disorder but showed a trend toward superiority in patients with bipolar II disorder [52]. Survival analysis (time to dropout for any reason) demonstrated LAM's superiority over placebo in the general cohort of patients and in those with bipolar II disorder but showed no significant separation from placebo in bipolar I patients. This study provides evidence for the role of LAM in rapid cycling subtype of bipolar disorder, particularly in bipolar II patients.

Dosing

LAM should be gradually titrated to minimize the probability of emergence of adverse events, particularly a serious rash. The recommended titration is: 25 mg/day for the first 2 weeks, then 50 mg/day for weeks 3 and 4, and then increasing by 50 to 100 mg/week to 200 mg/day or

as clinically indicated [53]. If LAM is part of a combination regimen involving CBZ, an inducer of LAM's metabolism, the starting dose of LAM should be doubled, and the titration should be more rapid. On the other hand, in a combination regimen involving DIV, the starting dose of LAM should be halved, and titration slowed, because DIV inhibits the metabolism of LAM (Table 2).

Tolerability

LAM is well tolerated and in placebo-controlled trials seems to be devoid of the polarity switches or cycle acceleration seen with antidepressants [50]. Headache, ataxia, dizziness, tremors, nausea, somnolence, diplopia, and blurred vision are the most common side effects reported with LAM [2,41–43]. LAM does not negatively affect weight, cognition, or sexual functioning [50]. In a published analysis of the rates of rash in 12 multicenter clinical trials involving 3153 patients exposed to LAM, 11.6% developed a benign rash, and less than 0.1% developed a serious rash [50]. Oral contraceptives (ethinylestradiol and levonorgestrel), when administered with LAM in an open-label, non–placebo-controlled study (n = 22), caused a significant decrease in serum levels of LAM (area under the curve by 52%; time to reach peak concentration by 39%) during the 21 days that the oral contraceptives where taken. By the end of the pill-free period, the trough concentration of LAM had increased by two times [53]. This interaction may decrease the efficacy of LAM when the use of oral contraceptives is initiated in a patient taking a steady dose of LAM. It may also increase the risk of rash during the pill-free period. The FDA originally described LAM as a pregnancy category C drug. The 2005 Interim Report of the International Lamotrigine Pregnancy Registry, however, reported data on the teratogenic potential of LAM based on the observed frequency of birth defects in patients with first trimester exposure to LAM monotherapy, which was 2.9% (95% confidence interval [CI], 1.6–4.9) compared with a background rate estimated at 2% to 3% [54]. The rate of birth defects among patients exposed to LAM and valproate cotherapy during the first trimester was 11.9% (95% CI, 6.6–20.2), compared with a rate of 2.9% (05% CI, 1.2–6.5) for patients receiving LAM polytherapy that did not

Table 2
Dosing of lamotrigine

	LAM alone	LAM + DIV	LAM + CBZ
Weeks 1 and 2	25 mg/d	25 mg every other day	25 mg two ×/d
Weeks 3 and 4	50 mg/d	25 mg/d	50 mg two ×/d
Week 5	100 mg/d	50 mg/d	100 mg two ×/d
Week 6	200 mg/d	100 mg/d	150 mg two ×/d
Week 7			200 mg two ×/d

Abbreviations: CBZ, carbamazepine; DIV, valproate or divalproex; LAM, lamotrigine.

include valproate as part of the treatment regimen. These preliminary data suggest that the rates of teratogenicity secondary to LAM exposure during the first trimester of pregnancy (2.9%) are similar to background rates in the epilepsy population (2%–3%) [54].

Topiramate

The mechanism by which TMP exerts its efficacy in epilepsy is not well understood. It affects the voltage-dependent sodium channels and GABA receptors and acts as an antagonist at the glutamate receptor. These varied actions may be responsible for its antiepileptic property, its potential effectiveness in bipolar illness, and possibly its action in substance abuse and eating disorders [3,55,56].

Acute efficacy

Acute mania

TMP has no efficacy, as a monotherapeutic agent in the treatment of acute mania, as demonstrated by five double-blind, placebo-controlled trials [56]. Some open-label studies and case reports have suggested a role for TMP in the treatment of acute mania, but its use in the treatment of acute mania is not recommended because it is not supported by the preponderance of controlled data.

Bipolar depression

An open-label study (n = 45) indicated that TMP (100–400 mg/day) may have some efficacy in the treatment of bipolar depression [1]. Nineteen of the 31 patients completing the study responded well to TMP, whereas 12 showed a partial response as measured by the HDRS. In a single-blind (rater blinded), randomized study, 36 currently depressed bipolar patients were assigned to receive either bupropion (50–300 mg/day) or TMP (100–400 mg/day) in addition lithium or DIV. TMP (56%) and bupropion (59%) demonstrated equivalent efficacy, based on a prior-response criterion of a 50% reduction on the HDRS [57]. Both TMP and bupropion were well tolerated, but patients taking TMP had greater weight loss than patients on bupropion.

TMP is associated with weight loss in psychiatric patients and in those with epilepsy. In a double-blind study involving patients with binge-eating disorder (n = 61), TMP (mean dose, 212 g/day) caused a significantly larger decrease in the frequency of binging and weight [3,56]. These data are promising, given the propensity of medications used in bipolar disorder to cause significant weight gain. TMP may play a critical role as an adjunct to a first-line mood stabilizer in minimizing weight gain associated with the primary mood stabilizers.

Maintenance efficacy

One large, open-label study (n = 58) has been conducted to assess the efficacy of TMP in the long-term management of bipolar disorder [58]. Patients with an index episode of mania received both TMP and risperidone. Risperidone could be discontinued at any point, but patients had to take TMP for 12 months to be considered study completers. Seventy-one percent of the patients completed the study. Substantial improvement was noted on the YMRS and the CGI-Bipolar Disorder scales. The rates of relapse during the 12 months of the study were lower than the rates seen in the previous year. Because of the lack of data from controlled trials, however, TMP should not be considered a primary option in the long-term management of bipolar disorder.

Dosing

Treatment with TMP should be started at 25 mg/day and titrated up by 25 mg every 4 to 7 days to a dosage range of 100 to 400 mg/day to minimize adverse events and enhance compliance.

Tolerability

Headache (32%), dizziness (24%), anxiety (24%), and dyspepsia (18%) were the most commonly reported adverse events in the controlled study in acute mania. Other common side effects seen with TMP are paresthesias, anorexia, nausea, diarrhea, headache, fatigue, and somnolence [1,55]. Cognitive difficulties and psychomotor slowing common and may be the limiting factors in either the use of TMP or its use at higher dose ranges. Nephrolithiasis occurs in 1% of the patients treated with TMP, with risk escalation associated with use of other carbonic anhydrase inhibitors such as acetazolamide and zonisamide [3]. TMP has not been associated with congenital malformations in humans (FDA pregnancy category C).

Gabapentin

GBP was developed as an analogue of GABA, the major inhibitory neurotransmitter in the human brain. It seems to bind to an amino acid transporter and acts at a unique receptor [55]. GBP does not act as a GABA precursor, agonist, or antagonist but increases the GABA levels in the brain and intracellularly by various mechanisms [59]. It also possesses a modulatory action on voltage-sensitive calcium channels [55]. Its low side-effect profile, coupled with its lack of drug–drug interaction and safety at high doses, make it a safe option in the treatment of bipolar disorder. Its use as a first-line agent in the treatment of acute and long-term bipolar illness, however, is limited by the lack of data from controlled studies.

Acute efficacy

Acute mania

The efficacy of GBP (600–3600 mg/day, flexible dosing) as add-on therapy to lithium or DIV was evaluated in a double-blind, placebo-controlled study with bipolar I patients (n = 117) in manic, hypomanic, or mixed states [60]. In the first phase of the study lasting 2 weeks, single-blind, flexible dosing of GBP was used versus single-blind placebo lead-in. This first phase was followed by 10-week, double-blind phase during which patients were randomly assigned to either GBP or placebo. Placebo demonstrated superiority over GBP on the primary efficacy measure, total decrease on the YMRS. The results of the study might have been confounded by non-compliance (20% of patients on GBP had undetectable plasma levels of the drug) and high rates of placebo response because of the larger proportion of lithium-dosage adjustment in patients taking placebo (75%, 9/12).

In another double-blind, placebo-controlled, crossover study comparing the efficacy of GBP monotherapy (up to 4800 mg/day), LAM (up to 500 mg/day), and placebo in treatment-refractory mood disorder in 35 in-patients for 6 weeks, GBP did not separate from placebo [59]. Of the patients who responded to GBP, response was associated with younger age, shorter duration of illness, and lower baseline weight.

Recommendation of GBP as an agent of choice or even as a first-line alternative in either acute mania or depression is not justified because of the lack of efficacy seen in controlled trials. Because of its anxiolytic properties [60,61], however, GBP may be used as an adjunct to first-line mood stabilizers in bipolar patients with comorbid anxiety disorders.

Maintenance efficacy

There is a paucity data from controlled trials assessing the efficacy of GBP in maintenance treatment of bipolar disorder. The use of GBP, as monotherapy in the long-term treatment of bipolar disorder is not recommended.

Dosing

GBP has a nonlinear bioavailability because the amino acid transporter responsible for its absorption in the gut and its transport through the blood–brain barrier is saturable. Plasma concentrations of GBP plateau at single doses higher than 1200 mg, three times a day. Treatment with GBP should be started at 300 mg/day and titrated to 900 mg/day within 3 days. GBP must be administered in three-times-per-day dosing [55].

Tolerability

GBP is generally well tolerated, has no active metabolite, and has minimal drug–drug interactions [59]. Common adverse events reported

include sedation, dizziness, drowsiness, ataxia, and dry mouth. GBP has an FDA pregnancy category C rating.

Zonisamide

ZON, an anticonvulsant with a structure similar to serotonin and a pharmacologic profile similar to CBZ, is thought to regulate the balance between inhibitory and excitatory amino acids in the brain by increasing the levels of GABA and by its antiglutamatergic properties [3,62]. Its blockade of voltage-sensitive sodium channels and reduction of voltage-dependent calcium channels may also play a role in its potential efficacy in bipolar illness [55]. ZON possesses weight-loss and sedative properties, characteristics that are seen in TMP as well.

Acute efficacy

Data from controlled studies evaluating the efficacy of ZON in acute mania or bipolar depression are lacking. An open-label study conducted in 1994 in 24 patients (15 with bipolar mania, 6 with schizoaffective mania, and 3 with schizophrenic excitement) demonstrated encouraging results, particularly in patients with bipolar mania [62]. It would be premature to conclude unequivocally that ZON is efficacious in acute mania because of the lack of evidence from rigorously controlled studies.

The most exciting aspect of ZON is its positive effect on weight. In a recent 16-week, double-blind, placebo-controlled study, ZON was significantly superior to placebo in causing mean weight loss (5.9 kg versus 0.9 kg) in obese nonpsychiatric adults. The superiority of ZON was even more substantial (9.2 kg versus 1.5 kg) when the study was continued in a single-blind extension for another 16 weeks [3,63]. These results are promising, because most drugs used in management of bipolar disorder (eg, the antipsychotics) cause weight gain, which negatively affects compliance. Given the ability of ZON to cause weight loss, it may have a role as an adjunct to other mood stabilizers when weight gain becomes the limiting factor in treatment compliance.

Dosing

ZON should not be administered to patients with allergy to sulfonamides, because ZON is a sulfonamide. Treatment with ZON is usually initiated at 100 mg/day and gradually increased by 100 mg every 2 weeks for a target dose of 100 to 600 mg/day [55].

Tolerability

The most commonly encountered side effects with ZON include sedation, dizziness, cognitive impairment, and nausea. These adverse events are

concentration and dose dependent and hence improve with dose reduction [55]. Renal calculi occur in about 1% of patients, and the risk may increase if ZON is administered in combination with other carbonic anhydrase inhibitors such as acetazolamide and TMP. CBZ, an enzyme inducer, decreases the serum level of ZON. ZON has not been reported to cause congenital malformations in humans (FDA pregnancy category C).

Levetiracetam

LEV is a novel anticonvulsant with a broad spectrum of efficacy in epilepsy. Its antikindling and neuroprotective properties make it an attractive option for treatment of patients with bipolar disorder. Its efficacy is thought to result from its effect on the GABA system [3,64].

There has been a case report of efficacy of LEV in bipolar disorder, and an open, add-on study with 10 patients showed LEV to exhibit antimanic properties [65]. Controlled studies are needed to investigate the role of LEV in the treatment of bipolar disorder.

Dosing

Treatment with LEV is initiated at 1000 mg/day in two divided doses, increasing by 1000-mg increments every 2 weeks to a maximum recommended dose of 3000 mg/day (1500 mg twice a day).

Tolerability

LEV is generally well tolerated. The most commonly encountered adverse events include sedation, fatigue, lack of coordination, and a decline in red blood and white blood cells. To minimize dose-dependent adverse events and to enhance compliance, treatment with LEV may be initiated at half the rate and titrated more gradually. LEV is not associated with congenital malformations in humans (FDA pregnancy category C).

Phenytoin

Like many other antimanic anticonvulsants, PHT blocks voltage-activated sodium channels limiting the spread of seizure activity and seizure propagation. This action may suggest a therapeutic role for PHT in the management of bipolar disorder.

Acute efficacy

Only limited and inconsistent evidence suggests a potential role for PHT in the acute management of bipolar mania despite early reports by Kalinowsky and Putnam [67] that PHT was markedly beneficial for acute

mania. Mishory and colleagues [68] reported a 5-week, double-blind, controlled trial of haloperidol plus PHT versus haloperidol plus placebo in 39 patients with either bipolar mania or schizoaffective mania. Significantly greater improvement was observed in the patients receiving PHT. Of note, additional improvements in scores on the Brief Psychiatric Rating Scale and CGI were seen in PHT-treated bipolar patients but not in the schizoaffective patients [68]. In a smaller sample of seven patients with mania, however, the intravenous administration of fosphenytoin (prodrug of PHT) did not produce any antimanic effects in any of the subjects during the 60 minutes of observation [69]. The dosing for fosphenytoin in this study is known to treat status epilepticus effectively, demonstrating its rapid onset of major neurobiologic effects, but it did not produce any beneficial effects for mania.

There are no data to support the use of PHT in the treatment of acute bipolar depression.

Maintenance efficacy

There is no evidence supporting PHT monotherapy for the prevention of mood episodes associated with bipolar disorder. Mishory and colleagues have reported a double-blind, placebo crossover study of PHT added to the ongoing mood stabilizing medication regimens of patients with bipolar disorder who had experienced at least one mood episode per year in the previous 2 years (Mishory et al, unpublished data). A significant prophylactic effect was observed with the addition of PHT, indicating a potential role for PHT as an add-on agent in patients with breakthrough mood episodes despite ongoing maintenance treatment with other agents. Replication of this study with a larger sample size is needed before acceptance of PHT's role in the long-term management of bipolar illness and to determine whether it possesses preferential prophylactic efficacy against the depressive or manic state of the illness.

Dosing

PHT should be avoided in individuals with a history of hypersensitivity to it or to other hydantoins. The dosing used in the Mishory et al study [64] (PHT, 100 mg/day as an add-on to other maintenance therapy) can be considered with 100-mg/day incremental increases each week to a target dose of 300 to 400 mg/day. Although a specific therapeutic blood range for bipolar disorder is not known, a potential target range of 10 to 20 μg/mL may be reasonable and is in line with the therapeutic blood range for epilepsy management and the blood levels observed by Mishory and colleagues.

Tolerability

The most common dose-dependent side effects reported with PHT therapy involve the central nervous system and include sedation, nystagmus,

fatigue, slurred speech, ataxia, coordination difficulty, confusion, dizziness, and headaches [55]. Rashes, including a risk for Stevens-Johnson syndrome, have been encountered. Hemopoietic complications of all varieties, with or without bone marrow suppression, have occurred and may be fatal. Nausea, vomiting, constipation, arthralgias, and gingival hyperplasia are less serious, although common, complications of PHT treatment and may cause discomfort for some patients.

Summary

In recent years, a number of anticonvulsants have been more rigorously investigated for their potential mood-stabilizing properties. They are heterogeneous in their mechanisms of action and in their efficacy in the various mood states in bipolar illness (Table 3).

At present, evidence from well-controlled studies supports the role of DIV and CBZ in the treatment of acute mania. DIV seems to have better efficacy than lithium in mixed mania or mania associated with depressive symptoms and is recommended as a first-line pharmacologic option in acutely manic or mixed manic patients [10]. Neither CBZ nor DIV have robust evidence supporting their efficacy in the treatment of acute bipolar depression, although DIV clearly possesses beneficial effects on depressive symptomatology and prophylaxis against depressive episodes during long-term treatment. Results from a large study indicate that LAM has significant efficacy in bipolar depression without the associated risks of cycle acceleration or manic/hypomanic switches. LAM should be considered a primary option in patients with bipolar depression and in bipolar II

Table 3
Comparative efficacy of anticonvulsants in bipolar disorder[a]

	DIV	CBZ	OXC	LAM	GBP	TMP	ZON	LEV	PHT
Classic mania	+++	+++	+	–	–	–	–	–	+/–
Mixed mania	+++	++	–	–	–	–	–	–	–
Bipolar depression	+	+	–	++	–	+	–	–	–
Rapid cycling, bipolar disorder I	++	+/–	–	+	–	–	–	–	–
Rapid cycling, bipolar disorder II	+	+/–	–	++	–	–	–	–	–
Prophylaxis	++	+	–	+++	–	+/–	–	–	+/–

Abbreviations: CBZ, carbamazepine; DIV, valproate or divalproex; GBP, gabapentin; LAM, lamotrigine; LEV, levetiracetam; OXC, oxcarbazepine; PHE, phenytoin or fosphenytoin; TMP, topiramate; ZON, zonisamide.

Symbols: +, limited controlled data supporting efficacy; ++, controlled data supporting efficacy; +++, replicated, controlled data supporting efficacy; +/–, small studies with controlled data supporting efficacy; –, no data or data does not support efficacy.

[a] Based on amount and strength of controlled data; scored relative to other anticonvulsants only.

patients with rapid cycling. DIV is recommended as a first-line option in bipolar I patients with rapid cycling.

LAM has proven efficacy in the prophylaxis of bipolar I disorder and should be considered along with lithium or DIV as treatment of choice in the long-term management of bipolar disorder. For the other anticonvulsants, including CBZ and OXC, there is still inadequate evidence of efficacy as monotherapy in the long-term management of bipolar disorder. Even less data exist for other available AEDs, and consensus is growing that some AEDs (eg, GBP) have little or no specific effect in bipolar disorder.

Despite the progress made in the past decade, a wider therapeutic armamentarium is critically needed, because a large proportion of bipolar patients do not respond to acute treatments during a manic or depressive episode and have frequent relapse and recurrences during long-term treatment. As additional AEDs become available, rigorously designed and large-scale studies examining AEDs as monotherapy and AEDs in combination therapies versus placebo must be undertaken to assess efficacy and safety more adequately to provide better guidance for the clinician faced with the management of this challenging mood disorder.

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